REMARKS

Amendment to the Claims

Applicant has cancelled withdrawn claims 1-11. Applicant reserves the right to pursue the subject-matter of these claims in a divisional application.

Applicant has re-written claims 12, 15, 16 and 17 in independent format. Claim 13 has been cancelled and the limitations of claim 13 have been added to claims 12 and 15. Claim 14 has been amended in light of the amendment to claim 12.

Claims 12 and 14-20 will be pending after entrance of this Amendment to the Claims.

Information Disclosure Statement

A Supplemental Information Disclosure Statement is being filed herewith that cites *inter alia* English counterpart patent documents for all non-English patent documents cited in the Information Disclosure Statement filed November 19, 2004.

Claim objection

The Examiner objected to claims 13 and 14 for being substantial duplicates. Applicant respectfully disagrees. Claim 14 recites a subset of the cancers in claim 13 (now listed in claim 12) and is therefore an appropriate dependent claim.

Rejection for lack of written description

Claims 12-20 were rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. The Examiner's argument appears to be based on a misconception that the claim term "c-Kit kinase" refers to a kinase family. Applicant respectfully notes that c-Kit kinase is a single tyrosine kinase. A copy of the GenBank entry for c-Kit kinase (Accession No. NM_000222) is included in the Supplemental Information Disclosure Statement filed herewith. Applicant therefore respectfully submits that the specification and knowledge in the art (e.g., GenBank Accession No. NM_000222) provide adequate written description for the claim term "c-Kit kinase." The person of ordinary skill in the art would appreciate that Applicant was also in possession of mutants of c-Kit kinase (i.e., a

mutant c-Kit kinase with mutations as compared to GenBank Accession No. NM_000222). The specification and knowledge in the art (e.g., GenBank Accession No. NM_000222) clearly define the structural features that are commonly possessed by members of this genus. To further support this, Applicant has included the following references in the Supplemental Information Disclosure Statement which is being filed herewith as evidence that mutants of c-Kit kinase we were known in the art at the time of filing:

- Longley et al., "Classes of *c-KIT* activating mutations: proposed mechanisms of action and implications for disease classification and therapy" *Leukemia Research* 25:571-576 (2001).
- Boissan et al., "*c-Kit* and *c-kit* mutations in mastocytosis and other hematological diseases" *J. Leukocyte Biol.* 67:135-148 (2000).
- Heinrich et al., "Inhibition of KIT tyrosine kinase activity: A novel molecular approach to the treatment of KIT-positive malignancies" *J. Clin. Oncol.* 20:1692-1703 (2002).

Besides, as noted above, Applicant has amended claims 12 and 15 to recite the specific cancers of cancelled claim 13. Applicant respectfully submits that the rejection for lack of written description should therefore be withdrawn.

Rejection for lack of enablement

Claims 12-20 were rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the enablement requirement. The Examiner's argument appears to be based on the premise that the experimental results presented in the specification are not sufficiently predictive to support the claimed *in vivo* methods. Applicant respectfully disagrees.

Example 1 of the present application describes *in vitro* cell proliferation inhibition results that were obtained with four different compounds using a small cell lung cancer cell line expressing c-Kit kinase (H-526). Example 2 describes additional *in vitro* experiments with one of these compounds which demonstrate that it inhibits c-Kit kinase phosphorylation. Significantly, Examples 3 and 4 then demonstrate that the *in vitro* results of Example 1 and 2 are reproducible in an *in vivo* mouse model. Thus, not only does the specification actually describe *in vivo* results, it also undermines the Examiner's premise that *in vitro* results are weakly

predictive of *in vivo* applications in the context of the presently claimed invention.

Applicant respectfully notes that the specification also compares the results that were obtained with these exemplary compounds against those obtained with other known c-Kit kinase inhibitors. In particular, the results demonstrate that the compound tested in Examples 3 and 4 was more potent than the c-Kit kinase inhibitor STI571 (Gleevec®) which has been approved by the FDA for the treatment of chronic myelogenous leukemia (CML) and gastrointestinal stromal tumors (GISTs).

As further evidence that the claimed methods are enabled by the specification, Applicant is filing herewith a Declaration under 37 CFR 1.132 by one of the co-inventors describing experiments using *in vitro* and *in vivo* models for gastrointestinal stromal tumors (GISTs). As demonstrated in the Declaration, the compound of Examples 3 and 4 inhibited c-Kit kinase phosphorylation in a GIST cell line expressing c-Kit kinase (GIST882) and this result was again reproducible *in vivo*. In light of these results and those provided in the application, Applicant respectfully submits that the rejection for lack of enablement should be withdrawn.

Rejection for indefiniteness

Claims 12-20 were rejected under 35 U.S.C. § 112, second paragraph as being indefinite as a result of the claim term "c-Kit". Applicant respectfully submits that "c-Kit" is not an acronym/abbreviation with many different meanings in the art as the Examiner suggests but is instead a formal name for a specific tyrosine kinase. The Examiner is again referred to the GenBank entry for c-Kit kinase (Accession No. NM_000222) which is included in the Supplemental Information Disclosure Statement filed herewith. The Examiner is also referred to the multitude of U.S. Patents that have issued with the term "c-Kit" in the claims (e.g., see U.S. Patent No. 7,211,600).

Rejection for obviousness

Claims 12-20 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Funahasi et al. (WO 02/032872) in view of Hibi et al. (*Oncogene* 6:2291-2296, 1991). Even if the cited references do teach what the Examiner suggests (which Applicant does not concede), the Examiner's argument is flawed since it relies on an erroneous logical assumption.

Specifically, the Examiner states that:

- Hibi et al. teaches that c-Kit kinase is expressed in small cell lung cancer; and
- Funahasi et al. teaches that the elected compound:
    - inhibits tumor cell proliferation; and
    - can be used as a "pulmonary treatment agent."

The Examiner then seems to argue that it would have been obvious to treat the small cell lung cancer of Hibi et al. with the elected compound of Funahasi et al. because: "Hibi et al. teaches that c-Kit expression is found in small cell lung cancer and Funahasi et al. teach the elected compound as an effective treatment for pulmonary treatment." However, if c-Kit expression in small cell lung cancer is the source of motivation for using the elected compound to treat small cell lung cancer, then there must also be some *express* teaching in the prior art that the elected compound inhibits c-Kit kinase. The Examiner's reliance on the *inherent* properties of the elected compound to combine the prior art references is improper since this inherent property is not disclosed in the prior art.

In addition, the Examiner cannot presume that because c-Kit is expressed in small cell lung cancer and because the elected compound is taught as a "pulmonary treatment agent" in Funahasi et al. then it must be acting as a c-Kit kinase inhibitor in Funahasi et al. Indeed, therapeutic agents for lung cancers do not necessarily show c-Kit kinase inhibitory activity. For example, Iressa® (Gefitinib or ZD1839) which can be used to treat non-small cell lung cancer is an EGFR-TK (epidermal growth factor receptor-tyrosine kinase) inhibitor (e.g., see Wakeling et al., *Cancer Research,* 62: 5749-5754 (2002), Naruse et al., *Int. J. Cancer*, 98: 310-315 (2002) and Ciardiello et al., *Int. J. Cancer*, 98: 463-469 (2002) which are provided in the Supplemental Information Disclosure Statement filed herewith). The same is true of Tarceva® (Erlotinib). If the presently claimed invention is obvious in view of the cited references, then it would logically follow that Iressa® and Tarceva® must also have c-Kit kinase inhibitory activity. However, it is uncertain whether Iressa® and Tarceva® have c-Kit kinase inhibitory activity. In other words, a person of ordinary skill cannot predict which therapeutic agents show c-Kit kinase inhibitory activity among therapeutic agents for lung cancer. Therefore, it would not have been obvious to a person of ordinary skill that because c-Kit is expressed in small cell lung cancer and because the elected compound is taught as a "pulmonary treatment agent" in Funahasi et al. then it must

be acting as a c-Kit kinase inhibitor in Funahasi et al. For all of these reasons, the Examiner's obviousness argument is flawed and should be withdrawn.

Conclusion

Applicant respectfully submits that the amended claims are in condition for allowance. If it is believed that a telephone conversation would help further expedite allowance of this case, or if any further information is required, the Examiner is invited to contact the undersigned at (617) 248-4793. Additionally, please charge any fees that may be required, or credit any overpayment, to our Deposit Account No. 03-1721.

Respectfully submitted,

Date: April 4, 2008

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